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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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MORGAN & FINNEGAN, L.L.P.
345 Park Avenue
New York, NY 10154-0053

EXAMINER	
YU, MISOOK	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 12/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/015,728	GELBER, COHAVA	
	Examiner	Art Unit	
	MISOOK YU, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12,14-21,35-39 and 49* is/are pending in the application.

4a) Of the above claim(s) *5,6,20 and 21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4, 7-12,14-19,35-39 and 49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *03/30/02, 01/17/03*, 12/02/04
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *inteview summary*.

DETAILED ACTION

Election/Restrictions

Applicant's election of group I drawn to monoclonal antibody, hydroma cell line producing said antibody, pharmaceutical comprising said antibody, encompassing claims 1-12, 14-21, 35-39, and 49 drawn in the reply filed on 09/29/2004 is acknowledged.

Upon review and reconsideration, the group I in the Restriction Requirement mailed on 06/03/2004 includes two different inventions (see the attached interview summary).

Claims 1-12, 14-21, 35-39, and 49 are pending and restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-4, 7-11, 12 (partially), 14-19, 35-36 (partially), 37, 38-39 (partially), and 49 (partially) to monoclonal antibodies and fragment thereof, which binds to 200 kDa antigen expressed on SCLC cells, producing hybridoma cell lines producing said antibodies, pharmaceutical comprising antibody, classified in class 530, subclass 388.1.

2. Claims 5, 6, 12 (partially), 20, 21, 35-36 (partially), 38-39 (partially), and 49 (partially), drawn to monoclonal antibodies and fragment thereof, which binds to 35 kDa antigen expressed on SCLC cells, producing hybridoma cell lines producing said antibodies, pharmaceutical comprising antibody, classified in class 530, subclass 388.1.

The inventions are distinct, each from the other because of the following reasons:

Inventions I, and II are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the two different inventions are different products they binds to two different antigens with different structural characteristics.

During a telephone conversation with Ms. Melissa Wenk on 12/21/2004 a provisional election was made with traverse to prosecute the invention of group I, claims 1-4, 7-11, 12 (partially), 14-19, 35-36 (partially), 37, 38-39 (partially), and 49 (partially),drawn to the200 kDa antigen specific monoclonal antibodies, and hybridoma cells producing said antibodies. Affirmation of this election must be made by applicant in replying to this Office action. Claims 5, 6, 20, and 21 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Claims 1-12, 14-21, 35-39, and 49 are pending, and claims 1-4, 7-12, 14-19, 35-39 and 49 are examined on merits to the extent as claims 12, 35-36, 38-39, and 49 are drawn to 200 kDa antigen specific antibody.

Claim Objections

Claims 12, 35-36, 38-39, and 49 are objected to because of the following informalities: the claims are drawn to multiple inventions. Appropriate correction is required. This objection would be obviated by amending the claims to reflect the election.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2, 7-12, 15-19, 35-39, and 49 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This enablement rejection has two aspects.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

First, claims 2, 7-12, 15-19, 35-39, and 49 recite specific monoclonal antibodies and hybridoma cell lines. It is apparent that the recited cell lines are required to practice the claimed invention, because they are specifically required in the claims. As required elements they must be known and readily available to the public or obtainable by a repeatable method set forth in the specification, or otherwise readily available to the public. If it is not so obtainable or available, the enablement requirements of 35 U.S.C. §

112, first paragraph, may be satisfied by deposit of the cell lines listed in claim 7. See 37 CFR 1.802.

The specification does not provide a repeatable method for obtaining the recited cell lines, and they do not appear to be readily available material. Deposit of the cell lines would satisfy the enablement requirements of 35 U.S.C. 112. While the specification states at page 7, 2nd paragraph that the cell lines "have been deposited" but the specification does not indicate the terms of the deposit.

If a deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made under the terms of the Budapest Treaty and that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, would satisfy the deposit requirements. See 37 CFR 1.808.

If a deposit is not made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made at an acceptable depository and that the following criteria have been met:

(a) during the pendency of this application, access to the invention will be afforded to one determined by the Commissioner to be entitled thereto;

(b) all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon granting of the patent;

(c) the deposit will be maintained for a term of at least thirty (30) years and at least five (5) years after the most recent request for the furnishing of a sample of the deposited material;

(d) a viability statement in accordance with the provisions of 37 CFR 1.807; and

(e) the deposit will be replaced should it become necessary due to inviability, contamination or loss of capability to function in the manner described in the specification.

In addition the identifying information set forth in 37 CFR 1.809(d) should be added to the specification. See 37 CFR 1.803 - 37 CFR 1.809 for additional explanation of these requirements.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If a deposit is made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the biological material described in the specification as filed is the same as that deposited in the depository, stating that the deposited material is identical to the

biological material described in the specification and was in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re Lundak, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR 1.801-1.809 for further information concerning deposit practice.

The second part of rejection has to do with the preamble "pharmaceutical" in claims 35-37, and 49. The specification teaches that several monoclonal antibodies were made using small lung cancer carcinoma (SCLC) cells, and the claimed antibody appear to react to an antigen of about 200 kDa (in fact between molecular markers of 120, and 213 kDa according to Fig. 8B) determined by SDS-PAGE gel. The specification at page 43 states that one of skill would be able to determine the dosage and able to use the claimed invention as pharmaceutical.

Krueger et al., (2003, Cancer Immunol Inmmunother vol. 52, pages 367-377) teach that "[a]ntibody internalization is crucial for use of small molecule drugs or use of immunotoxins in immunoad[a]ptive therapy." The specification at paragraph [0119] discloses that the monoclonal antibody MoAb 51.2 is internalized by a SCLC cell line cells. However, the specification does not discloses that whether any of the claimed monoclonal antibodies produced by the specifically recited hybridoma cell lines could be internalized by any in vivo SCLC cells.

The art acknowledges that cancer cell lines in vitro culture and cancer cells in vivo behave differently. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, page 4) teach that it is recognized in the

art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, Dermer (Bio/Technology, 1994, 12:320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary - type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not, yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions. Thus, based on the cell culture data presented in the specification, it could not be predicted that either MoAb 51.2 antibody or any of other instantly claimed antibody would work *in vivo*. It is the Office's position that screening monoclonal

antibodies using in vivo subjects requires undue experimentation. It is noted that law requires that the disclosure of an application shall inform those skilled in the art how to make and use the alleged discovery, not how to screen it for themselves.

Considering the unpredictable state of art, limited guidance, no examples in the specification how to use the instantly claimed invention as pharmaceutical, broad breath of the claims, it is concluded that undue experimentation is required to practice the invention.

Claims 1, 3, 8, 10, 11, 14, 18, 35-39, and 49 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This written description rejection is made because claims 1-12, 14-21, 35-39, and 49 are interpreted as drawn to a genus of monoclonal antibodies binding to an antigen whose structure is not in the claims, and a genus of hybridoma cells producing said antibodies.

The applicable standard for the written description requirement can be found: MPEP 2163; University of California v. Eli Lilly, 43 USPQ2d 1398 at 1407; PTO Written Description Guidelines; Enzo Biochem Inc. v. Gen-Prove Inc., 63 USPQ2d 1609; Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111; and University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC 2004).

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. This rejection is about the claims failing to provide an adequate written description of the antigen. The only factor present in the claim for the antigen that the instantly claimed monoclonal antibodies is that it is a single polypeptide with a molecular weight of about 200 kDa and a positive expression on SCLC, negative expression on two cancers other than SCLC. The structure of polypeptide is a string of amino acids. The expression profile of the antigen is not the function of the antigen. Many different antigen appear to be expressed in SCLC (note page 7 left column of Rose et al., cited below). Further, it appears that glycosylation status changes the molecular weight of a single antigen (note Table 1 of Rose et al.) although it is the same antigen. In the absence of the primary structure(s) of the antigen(s), disclosing four monoclonal antibodies to broad antigen(s) is disclosing a representative number of species. Therefore, it is concluded that applicant adequately describes Moab 51.2, 37.14, 109.12, 26.1.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3, 8, 10, 11, 14, 18, 35-39, and 49 are rejected under 35 U.S.C. 102(b) as being anticipated by Rose et al., (#3 IDS filed on 12/02/2004, 1994 Hybroma vol. 13, pages 221-227).

Claims 1, 3, 8, 10, 11, 14, 18, 35-39, and 49 are interpreted as drawn to a monoclonal antibody (claims 1, 3, 8, 10, 11, 14, 18, 38, 39, and 49), and hybridoma cells producing said monoclonal antibody (claim 14), wherein said antibody binds to an antigen expressed on the surface of SCLC, wherein the said antigen is characterized to be about 200 kDa as determined by SDS-PAGE under reducing conditions, glycosylated, absent from human multiple myeloma cells (claims 1, 3, 14), wherein a monoclonal antibody capable of binding to the same antigenic determinant as do the recited monoclonal antibodies (claim 8) wherein the antibody of claim 8 is present on human small cell ling cancer cells and absent from human multiple myelama cells, (claim 10), wherein the antibody binds to a single chain polypeptide having a molecular weight of about 200 kDa as determined by SDS-PAGE under reducing conditions, wherein the single chain polypeptide is glycosylated (claim 11), wherein the antibody is in a pharmaceutical composition comprising a pharmaceutically acceptable carrier (claim 35-37, and 49), wherein the antigen is absent from neuroendocrine cells, wherein the antibody is labeled with a detectable moiety (claim 38), and wherein said detectable moiety is a label commonly used in the art for detection (claim 39).

Rose et al., teach to CR101 monoclonal antibody and hybridoma producing CR101 (note the title and abstract), wherein said antibody binds to an antigen

expressed on the surface of SCLC (note Fig. 7, and Table 2), wherein the said antigen is characterized to be about 200 kDa as determined by SDS-PAGE (note Fig. 4), glycosylated (note Table 1), wherein the antibody binds to a single chain polypeptide having a molecular weight of about 200 kDa as determined by SDS-PAGE (note Table 1, wherein the antibody is labeled with a detectable moiety (note the heading "ELISA" at page 222, and "FACS analysis" at page 223), wherein said detectable moiety is a label commonly used in the art for detection (page 222, and "FACS analysis" at page 223), wherein the purified antibody i.e.CR101 is in "PBS" (note page 222, right column, line 9 under the heading "Western blot ana[l]ysis").

As for the limitation "absent from human multiple myeloma cells", "absent from neuroendocrine cells", "monoclonal antibody capable of binding to the same antigenic determinant as do the recited monoclonal antibodies", the Office does not have the facilities and resources to provide the factual evidence needed in order to establish that the antibody, hybridoma, pharmaceutical composition of the prior art does not possess the same material, structural and functional characteristics of the instantly antibody, hybridoma, pharmaceutical composition. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed composition is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

As for the limitation "under reducing conditions" in claim 1, Rose et al., teach that the SDS gel, but does not mention that the SDS gel was run under reducing condition.

However, Voet et al., (1990, Biochemistry, John Wiley & Sons, page 98, and 99 only) teach at page 99, right column lines 5-6 that mercaptoethanol is usually added to SDS-PAGE gels so as to reduce disulfide bond. Since Rose et al., that the gel separated two different bands (note Figure 5 possibly due to different glycosylation states, also note Table 1), it is the Office's position that the gel was mostly likely run under the reducing condition.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rose et al., (#3 IDS filed on 12/02/2004, Hybroma vol. 13, pages 221-227) in view of Ward, ES (1992, Antibody Engineering, W. H. Freeman and Company, Car. A. K. Borrebaeck, ed, pages 122-123 only).

Claims 1, and 12 are interpreted as drawn to a Fab fragment made from the antibody of the base claim 1 (see the interpretation of claim 1 above).

As stated above in 102 (b) rejection, Rose et al., teach the monoclonal antibody with the characteristic described in the base claim 1.

Rose et al., do not teach the various art-known antibody fragments recited in claim 12.

However, Ward, ES (1992, Antibody Engineering, W. H. Freeman and Company, Car. A. K. Borrebaeck, ed, pages 122-123 only) teach at page 121 that Fab, and Fv had been known well before the effective filing date of the instant application, and Fab being made in E. coli has many advantages, such as less tedious process of making an antibody.

Therefore, it would haven obvious to one of ordinary skill to make Fav fragment of the monoclonal antibody of Rose et al., to make and use the Fab and other engineered antibody fragments with a reasonable expectation of success given the advantage associated with making the antibody fragments.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MISOOK YU, Ph.D. whose telephone number is 571-272-0839. The examiner can normally be reached on 8 A.M. to 5:30 P.M., every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey C Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MISOOK YU, Ph.D.
Examiner
Art Unit 1642

MISOOK YU
PATENT EXAMINER

MISOOK YU
PATENT EXAMINER